Report of a Review of Pathology Materials from Chronic Rodent Cancer Studies Carried out at the Ramazzini Institute, Italy (Pathology Working Group Report)

NIEHS/NTP Communications Strategy

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NIEHS/NTP will feature the Ramazzini Institute Pathology Review Report on the NTP web site (http://ntp.niehs.nih.gov/). No additional efforts will be made to raise awareness of this report.

The report will be posted to the NTP website upon approval from NIH and HHS leadership, in full coordination with the EPA. The report will be posted on XXXXXXXX.

NIEHS communications staff have worked with NIEHS/NTP staff to develop internal talking points and q's and a's. The report and materials are being shared with NIH Leadership, HHS, and EPA.

NIEHS/NTP staff will respond to media inquiries on an individual basis. The link to the report will be provided and if an interview is requested, the spokespersons will use the topline messages and Q&As below to respond.

Topline Messages

The Summary Report of the National Toxicology Program and Environmental Protection Agency-Sponsored Review of Pathology Materials from Selected Ramazzini Institute Rodent Cancer Bioassays is now available on NTP website at http://ntp.niehs.nih.gov/.

The Ramazzini Institute is based in Italy and conducts laboratory studies on chemicals to determine their carcinogenicity.

The NTP conducted a pathology working group (PWG) review of RI's methanol pathology data in the Spring of 2010. The EPA conducted a review to determine what impact the PWG's findings would have on ongoing and completed assesements.

Based on the Pathology Working Group review, NTP and EPA will not use Ramazzini Institute's data on lymphomas and leukemias in the future. The NTP and EPA will continue to use Ramazzini Institute data on solid tumors for several assessments. The NTP and EPA will use other Ramazzini data if there is first a pathology working group review of the data.

In the meantime, the PWG made several recommendations to RI for changes in laboratory procedures, which are already being implemented.

Potential Questions and Answers

1. What does the Pathology Working Group report say?

   The report says that, with the exception of leukemias and lymphomas, the pathology procedures and findings of the RI cancer studies are reliable and are in line with diagnostic criteria currently used by veterinary pathologists. The report pointed out some instances where the presence of respiratory infections in RI study animals made definitive diagnoses difficult, and that some RI diagnoses, primarily certain leukemias and lymphomas, were not considered to be neoplasias.

2. Who commissioned the Report? What was studied?

   The Pathology Working Group (PWG) was commissioned by NTP and EPA to conduct an independent pathology review for five rodent chronic cancer studies conducted by RI.
   - methanol,
   - methyl-*t*-butyl-ether (MTBE)
   - ethyl-*t*-butyl-ether (ETBE)
   - acrylonitrile
   - vinyl chloride (VC)

3. Was there agreement among the RI pathologists and the Pathology Working Group?

   The Pathology Working Group was in general agreement with the tumor diagnoses made by the RI pathologists in three of the studies (ETBE, acrylonitrile, and VC).

4. What were the differences in opinions?

   There were some differences in the diagnoses in the methanol and MTBE studies. The PWG found fewer malignant neoplasms than the RI pathologists. The differences may be related to the presence of inflammation caused by chronic respiratory infections in the animals which can make diagnosis difficult.

5. Who picked the studies to review and why?

   The studies that were reviewed by the PWG were studies mainly of interest to the EPA. These studies were included as part of the database of information evaluated by the EPA in routine chemical safety assessments.

6. The Summary Report document has a November date, why has it not been released until now?

   The Pathology Working Group was co-funded by the EPA, and they have been evaluating the implications of the findings for their chemical assessment programs.

7. What impact will these findings have on the NIEHS?

   There are no direct impacts of the report results on the NIEHS. The NIEHS has had a cooperative arrangement with the RI to compare and coordinate procedures and practices used in the conduct of long-term cancer studies. The PWG was an extension of those efforts. One of the recommendations from the review was that the RI routinely include a pathology review process comparable to that used by the NTP as part of their studies. This is already being implemented by RI.

8. What about the Report on Carcinogens? Is there any impact of these findings on the listings?

   The listings in the RoC would not change since the data from the Ramazzini Institute are only one of many sources used. In general, listings in the RoC are based on a large body of information and include findings from animal cancer studies carried out by many organizations. Based on our review of the listings, we do not believe the PWG findings will affect the listing status of any substance currently in the RoC. The rodent cancer bioassay data generated by the Ramazzini Institute (RI) are a small part of a larger body of data used by the NTP to make decisions on chemicals.

9. What about using Ramazzini data for the substances currently nominated for review in the next RoC?

   None of the substances nominated to the RoC have been studied by the Ramazzini Institute. A listing of the nominated substances is available at http://ntp.niehs.nih.gov/?objectid=C3213BD9-F807-E389-916C16858403102B

10. Has the NTP conducted studies on methanol?

    No, the NTP has not conducted any studies on methanol.

11. What are the implications of these findings for the EPA?

    REFER TO TOPLINE MESSAGES. Please contact the EPA for more information on how the PWG report may influence their assessments. .

12. Are the PWG results in any way binding on the RI? Will they be issuing amended publications for their results based on this report?

    The PWG report represents a consensus opinion of an independent group of pathologists. The report is in no way binding on the RI, and should be considered simply as a second opinion concerning certain of the findings from RI studies. If the RI wishes to act on any of the findings it's up to them.

Background

The Ramazzini Institute (RI) is a research laboratory in Bentivoglio, Italy that conducts animal testing to evaluate the potential cancer-causing effects of chemicals.

The NIEHS/NTP has had a series of agreements with the Ramazzini Institute over the years to coordinate cancer studies and training and to share methodologies and processes with respect to large rodent cancer studies.

In 2010 the NTP sent a small team of NTP pathologists to RI to conduct a preliminary review of pathology data for the rodent chronic bioassay used in the RI methanol study.

The review identified some differences in pathology diagnoses of lymphoid neoplasms and inner ear and cranial neoplasms.

Based on these preliminary findings, the NTP and US Environmental Protection Agency (EPA) proposed that five RI chronic rodent cancer studies be subjected to an independent pathology review.

The five studies selected were methanol, methyl-*t*-butyl-ether (MTBE), ethyl-*t*-butyl-ether
(ETBE), acrylonitrile, and vinyl chloride (VC).